DIABETES & PREGNANCY

Diabetes Complicating Pregnancy

- **Gestational Diabetes**
- **Pre-existing Diabetes**
- Each is uniquely defined
- Share some common risks including macrosomia, C-section
- Fetus exposed to high glucose environment develops other complications after delivery including infant respiratory distress syndrome, cardiomyopathy, hypoglycemia, hypocalcemia, hypomagnesaemia, polycythaemia and hyperviscosity syndrome

Diabetes Complicating Pregnancy

- HAPO study (hyperglycemia and adverse pregnancy outcome)
  - 25000 pregnant women in 15 centers - even sub clinical hyperglycemia resulted in obesity, metabolic syndrome or both compared with children born for known diabetic mothers
- New England Journal of Medicine 2008 - 358
- Pre-existing diabetes carries additional risks: congenital malformations in infant and maternal risks related to complications.

Normal Physiology of Pregnancy

- First trimester-Increased insulin sensitivity.
- Late 2nd and 3rd trimester insulin resistance possibly associated with increasing levels of human placental lactogen (hPL) which correlates with placental mass.
- hPL shares 87% of its amino acids with human growth hormone.

Fetal Effects

- Glucose travels freely from mother to fetus
- Maternal insulin does not
- So maternal diabetes exposes fetus to high levels of glucose
- Fetus increases its own insulin production
- So increased fetal growth resulting in weight exceeding 4000-4500gm referred to as macrosomia

Gestational Diabetes

- Definition – carbohydrate intolerance of varying severity with 1st recognition of onset occurring during pregnancy.
- Complicates 4% of all pregnancies. Prevalence varies from 1 – 14% depending on the population.

Pathophysiology of GDM

- GDM is characterized by a reduction in 1st phase insulin release in response to iv glucose.
- Alterations in insulin sensitivity, fat, carbohydrate, amino acid metabolism may also occur.

Screening for GDM

- ADA recommends selective screening
- ACOG recommends either selective or universal

STAGE I SCREENING

1. 50 gm glucose load
   1 hour value - ≥ 130 – 140 - 90% sensitivity
   This indicates Gestational Diabetes
2. Confirm by 100gm 3 hour oral glucose tolerance test
3. WHO recommends 75gm GGT at 24-28 weeks

High Risk

- Obesity (> 20% above BW)
- Previous history of GDM
- Glycosuria
- Strong family hx of DM (1st degree relative)
- Impaired OGTT or IFG
- Previous baby with > 9 lb birth weight.

High Risk Screening

- Timing – " as soon as feasible"
- Repeat at 24 – 28 weeks if initial screen is negative or sooner if symptoms of glycosuria develop

Evaluate women with pregestational diabetes for diabetic complications before conception and review issues of diabetic control, and review symptoms of hyperglycemia in all pregnant women

- Screen pregnant patients with no previous history of diabetes for hyperglycemic symptoms.
- Assess history of acute diabetic complications.
- Review history of retinopathy, nephropathy, hypertension, atherosclerotic disease, and neuropathy.
- Review duration and type of diabetes and current diabetes management.
- Document other concomitant medical conditions and drugs.
- Review basic pregnancy issues, such as past pregnancy history, menstrual history, and support system for the patient.
- Obtain dilated retinal exam before pregnancy.
- Measure blood pressure and test for orthostatic changes.
- Perform cardiovascular exam to look for evidence of cardiac or peripheral vascular disease.

Use laboratory testing to evaluate diabetic control and to screen for related medical conditions

- Obtain the following in women with pregestational diabetes before conception:
  - HbA1c level
  - 24-hour urine test for protein and creatinine levels
  - ECG
- Obtain blood glucose level in all pregnant women:
  - In the first trimester or at the first prenatal visit
  - With symptoms of hyperglycemia, to monitor for the development of diabetes
- Check thyroid levels with the first set of antepartum labs in patients with type 1 diabetes.

Switch all women with pregestational diabetes on oral diabetic treatments to insulin before conception

- Stop all oral diabetic medication 3 months before conception.
- Use insulin in all pregnancies requiring medication for glucose control.

Stop ACE inhibitor therapy and review the patient's other medications before conception

- Do the following before conception:
  - Stop all ACE inhibitors and angiotensin receptor blockers
  - Stop cholesterol-lowering drugs
  - Stop aspirin therapy
- Review other medications and stop potential teratogens

Drugs to Avoid in Pregnancy

Agent	Mechanism of action	Dosage	Benefits	Side Effects	Notes
ACE inhibitor	Blocks the conversion of angiotensin I to angiotensin II	Variable 5–40 mg/d	Do not use in pregnancy	Fetal teratogen	Screen for ACE inhibitor use in premenopausal diabetic patients and stop before conception
Angiotensin receptor blocker	Blocks angiotensin II receptor sites	Variable 25–100 mg/d	Do not use in pregnancy	Fetal teratogen	angiotensin receptor [illegible] premenopausal diabetic [illegible] fore conception
Aspirin	Cyclo-oxygenase inhibitor	81–325 mg/d	Do not use in pregnancy	Maternal and newborn hemorrhage, increased perinatal mortality, intrauterine growth retardation, and teratogenic effects	In one [illegible] 3 of 14 newborn [illegible] in 1 week of deli[illegible] hemorrhaging controls(18). In studies, mothers [illegible] infants were deliv[illegible] aspirin during pregn[illegible] frequently than moth[illegible] infants (11:12)
HMG-CoA reductase inhibitor	Decreases synthesis of cholesterol in the liver	Variable	Do not use in pregnancy	Possible teratogen	In a surveillance study o[illegible] exposure during pregnan[illegible] outcomes were: 85% norm[illegible] anomalies 4.8% spontaneo[illegible] abortions 8.8% and fetal d[illegible] stillbirths 1.0% (9)

Non-drug Therapy

- **Stress** diet and exercise in pregnant diabetic patients to control glucose levels.
- **Continue** foot care in women with pregestational diabetes.
- **Recommended** smoking cessation in all women with diabetic pregnancies
- Consider recommending to pregnant diabetic patients
  - A calorie restriction of 30% to 33% in pregnant women with diabetes and a body mass index >30
  - Limiting carbohydrate intake to 35% to 40% of calories
- A program of moderate exercise
- Home blood glucose monitoring – before breakfast and 2 hours post meals
- Am urine ketone monitoring

Drug Therapy

- **Use** insulin in patients with gestational diabetes to achieve optimal glycemic control.
- **Switch** all women with pregestational diabetes on oral diabetic treatments to insulin before conception.
- **Stop** ACE inhibitor therapy and review the patient's other medications before conception.

Use insulin in patients with gestational diabetes to achieve optimal glycemic control

- Adjust insulin doses to achieve fasting whole-blood glucose levels of 70 to 100 mg/dL and 2-hour postprandial levels of <140 mg/dL

Insulin in Diabetes and Pregnancy

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Insulin Aspart NOVORAPID Lispro	Protein hormone that regulates glucose metabolism	As needed	Reduced Postprandial hyperglycemia Short onset of action, rapid acting, reduces postprandial hyperglycemia	Hypoglycemia, Hypokalemia, Injection Site reactions, lipodystrophy	Patient satisfaction in one study favored insulin Aspart with long acting insulin over insulin
Insulin regular	Protein hormone that regulates glucose metabolism	As needed	Short-acting	Hypoglycemia, Hypokalemia injection –site reactions, lipodystophy	Mo... injec... for ti...
Insulin neutral protamine Hagedorn	Protein hormone that regulates glucose metabolism	As needed	Intermediate acting	Hypoglycemia, Hypokalemia injection –site reactions, lipodystophy	May Use without th... acting in...

Insulin in Diabetes and Pregnancy

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Glargine to be avoided in pregnancy					
Folic Acid	Vitamin supplementation	400ug/d to 1.0 mg/d	Reduces fetal neural tube defects	Nausea, abdominal, malt, anorexia	Ideally began before conception
Metformin	Increases insulin sensitivity	500-2,000 mg/d	May decrease the incidence of gestational diabetes among women with polycystic ovarian syndrome	Inadequately controlled blood glucose levels, lactic acidosis, diarrhea, nausea, and vomiting	ovu... takin... befor... and th... pregnan... 10-fold ... in the ... developm... gestationa... diabetes (...

Insulin Analogs (NOVORAPID)

NovoRapid® treatment resulted in:

- 52% lower risk of major nocturnal hypoglycaemia (p=0.096) with similar overall glycaemic control
- Superior postprandial glycaemic control
- No concern with regards to progression of diabetic retinopathy

Insulin Analogs (NOVORAPID)

NovoRapid® treatment resulted in:

- Similar pregnancy outcome with regards to:
  - Fetal loss
  - Congenital malformations
  - Macrosomia as human insulin
- A trend towards:
  - Fewer preterm deliveries (p=0.053)
  - Lower birth weight
  - Fewer neonatal hypoglycaemic episodes

Insulin Analogs (NOVORAPID)

With NovoRapid® treatment, there was:

- No increase in cross-reacting insulin antibodies
- No evidence of transfer of insulin Aspart across the placenta
- Better overall treatment satisfaction

Insulin Analogs (NOVORAPID)

- NovoRapid® is at least as safe and efficacious as human insulin in pregnant women with Type 1 diabetes

- The benefit to risk ratio is favourable for use of NovoRapid® in pregnant women with diabetes

NOTE

- Joslin Clinic - 2004 recommended human insulin and placed Lispro in category B and Aspart and Glargine in category C
- Current literature says that Aspart and Lispro are both safe - Lancet May 2009

Management Of GDM during labor, delivery and postpartum

- Induction – Normal insulin dosage day before
- Omit morning insulin day of induction
- Maintain plasma glucose 80 – 110 mg/dl with iv dextrose and insulin infusion
- Postpartum – No insulin required (usually).

Monitor prebreakfast and 2 hour post meal blood sugars for 24 hours. Perform 75mg 2 hour OGTT at 6 weeks post partum. Counsel on high risk of progression to T-II Diabetes. (50% after 20 years). Recommend dietary and exercise modifications based on Diabetes Prevention Program to reduce future risk (by 60%).

Pre-existing Complications of Diabetes in Pregnancy

Baseline Level of Retinopathy

Predicts Risk of Progression During Pregnancy

- Mild noo-proliferative
  - Changes during pregnancy are minimal and return tobaseline pospartum
- Moderate to severe non-proliferative
  - Progression to proliferative retinopathy occurs in 10 –25% especially with more severe disease. Severe NPDR should stablized with laser prior to pregnancy or in the 1st trimester
- Proliferative
  - High risk of progression. Stabilize preconception.
- Proliferative in remission
  - Rarely associated with reactivation.

Gastroparesis

- Exacerbated by morning sickness and mechanical compression by an enlarging uterus.
- May Undermine glycemic control during pregnancy and potentiate the risk of severe hypoglycemia.
- Rarely has been associated with significant maternal morbidity (need for TPN)
- Pregnancies in patients with severe gastroparesis are unusual but are likely to be associated with worsening of symptoms.

Nephropathy

- Urinary albumin excretion rates increase dramatically. Nephrotic range proteinuria may be observed.
- Returns to baseline postpartum.
- Pregnancy does not seem to alter the natural history of diabetic nephropathy except in
- Women with creatinine > 2 – 3 mg may not be able to support a pregnancy

Review diabetes drugs after delivery and make changes as necessary

- Adjust insulin in patients with type 1 pregestational diabetes post delivery according to multiple, daily blood glucose testing to maintain hemoglobin A1c at <7%.
- Stop insulin in women with gestational diabetes after delivery and monitor glucose levels.
- Consider the reinstitution of oral diabetes medication in women with type 2 pregestational diabetes post delivery unless patient is nursing.

Counsel all diabetic women of childbearing potential on the need for pregnancy planning

- Ensure effective birth control at all times, unless the patient is trying to conceive and is in good diabetic control.
- Counsel women with type 1 or 2 diabetes on the risks of fetal malformation associated with unplanned pregnancies and poor metabolic control.
- Achieve fasting whole-blood glucose levels of 70 to 100 mg/dL and 2-hour postprandial levels of <140 mg/dL in diabetic women planning pregnancies.

Counsel all obese women of childbearing age on the need for diet and exercise to decrease the risk of gestational diabetes

- Provide nutritional counseling to obese women of childbearing age consistent with American Diabetes Association recommendations.
- Consider recommending to obese women planning pregnancy or already pregnant:
  - A 30% to 33% calorie restriction if BMI >30
  - Limiting fat intake to <30% of calories
- Increasing physical activity, as recommended outside pregnancy, or a program of moderate exercise if the woman is already pregnant

Plan future pregnancies postpartum

- Recommend birth control immediately postpartum.
- Stress the importance of pre-conception counseling.

After delivery, classify patients found to be diabetic during pregnancy and arrange for long-term follow-up

- Continue home glucose monitoring in women found to be diabetic during pregnancy at least 6 weeks postpartum to determine if they have underlying type 1 or 2 diabetes or if their hyperglycemia resolves.
- Counsel patients with transient gestational diabetes on the long-term need for diabetes screening.
- Recommend nutrition and exercise consistent with American Diabetes Association guidelines to patients with transient hyperglycemia of pregnancy after delivery.